(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 525 273 A1**

(12) EUROPEAN PATENT APPLICATION

(21) Application number: **91500089.7**

(22) Date of filing: **02.08.91**

(51) Int. Cl.5: **G01N 33/49**, G01N 33/86, G01N 11/10

(43) Date of publication of application:
03.02.93 Bulletin 93/05

(84) Designated Contracting States:
BE DE ES FR GB IT NL

(71) Applicant: **GRUPO GRIFOLS, S.A.**
Poligono Levante, Can Guasch s/n
E-08150 Parets Del Valles, (Barcelona)(ES)

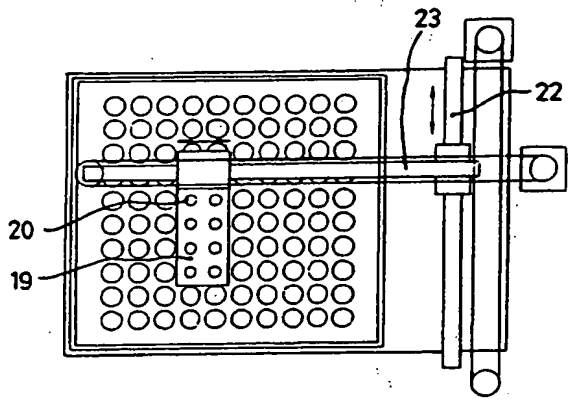
(72) Inventor: **Martinell Gisper-Sauch, Enrique**
Paseo San Juan, 34
E-08010 Barcelona(ES)
Inventor: **Gasull Llampallas, Antonio**
Enric Borras, 30, 4o 1a
E-08912 Badalona, (Barcelona)(ES)

(74) Representative: **Duran Moya, Luis-Alfonso et al**
c/o DURAN-CORRETJER Paseo de Gracia no. 101
E-08008 Barcelona(ES)

(54) Process and apparatus for the determination of the coagulation time of blood and plasma.

(57) Process and apparatus for the determination of the coagulation time of blood and plasma.
Comprises mechanical means contacting the fluid and the corresponding reactives to be analyzed, which mechanical means are given a displacement which is capable to be altered by the initiation of the coagulation of the fluid to be analyzed, wherein the images in real time of the mechanical means under displacement within the fluid to be analyzed are obtained by means of a television camera, being transmitted to a computer to analyze the images to derive from the same the variation of one or more parameters related with the alteration of the movement of the mechanical means as a function of the initiation of the coagulation.

FIG.8



EP 0 525 273 A1

One of the characteristics with a higher interest in the handling of blood and plasma for clinical purposes consists in the evaluation of the coagulation time.

Various processes and systems are known for this aim which are based on physical effects related to the formation of fibrine which is typical of the coagulation cascade.

Among the apparatus and systems already known, the optical and mechanical coagulation meters may be cited. Some of these systems comprise rotating bars, corresponding to optical type meters; other systems rely on a rotating ball with sensors based on the Hall effect, others are based on vibrating or oscillating webs combined with vibration sensors, other types are based on the variation of electrical conductivity between electrodes and finally, other systems rely on the measurement of the variations of capillary viscosity.

The automatized systems require in order to increase the velocity of the process to carry out a series of different measurements simultaneously. This may be carried out by the arrangement in parallel of a series of sensors or having the reaction wells to rapidly cross in front of a sole sensor.

In both cases, some limitations appear as to space or time in the practical embodiment of the process.

To find a solution to the above drawbacks, the process and apparatus of this invention are based on completely different and original principles, consisting basically in the determination of the moment in which the coagulation process is initiated, by evaluation of the variation of mechanical characteristics appearing in the fluid to be analyzed. Therefore, the principle is essentially of a mechanical nature, requiring a ball, bar or any other object which movement may be disturbed by the reaction. This change will be detected in form of the corresponding image by means of an image-taking camera, in order that the generated signal may be processed as a dynamic image with the detection, by means of a digitation process, of the moment in which the change in the movement of the mechanical object being displaced within the fluid to be analyzed takes place. The fluid preferably consists, as above stated, in plasma or blood.

The determination of the moment in which the coagulation initiates is carried out by means of a programmable computer in which a comparison will be made of the values of certain parameters which depend on the mechanical performance of the fluid being analyzed with a certain standard or pattern. Therefore, the camera for taking images of the process will be used only for the capture and relying of the generated signal to the computer.

Any parameter may be used for the determination of the moment in which coagulation starts, in order to compare its value with a certain model. Such parameter may be any parameter which depends on the variation of the mechanical characteristics of the fluid to be analyzed in the moment in which the changes in the coagulation appear, that is, the formation of fibrine. Preferably to be used will be certain parameters as angular speed, linear speed and the position, that is, the radius of rotation of the mechanical element related with the fluid being analyzed.

After experimental work, the inventors have found that the parameters which are more suitable to carry out the invention consist in the linear velocity and the radius of rotation, as the angular speed is practically maintained during all the process.

The advantages to be obtained with the detection system of the present invention consist mainly in that the detection system in itself may be separated from the place in which the reaction is carried out, requiring only a "point of vision" from which the image will be captured. This characteristic allows the gathering (for example on a rectangular flat surface) of the reaction wells or cavities, reducing in this way the space needed, as no individual detector for each reaction is necessary. At the same time, the new process will allow the processing of multiple reaction wells in parallel, without requiring the reactions to be simultaneous, as it is not needed that all reactions start at the same time, given the fact that the invention allows the separate processing of each of them. At the same time, as the detection is carried out by means of a programmable computer, it is very simple to proceed to the change of the detection parameters, which in extreme cases could be carried out by the computer itself in an "intelligent" manner.

Therefore, the invention permits to carry out the automatic detection of the occurence of coagulation with great capacity and in a short time in comparison with previously known systems.

The apparatus to carry out the process of the present invention will preferably comprise a plate for carrying the reaction wells or cavities, preferably made out of plastic material, having multiple wells or small cavities in which the reactions will be carried out. The external shape of the plate may be changed according to convenience. It may be simply rectangular, for example, with ten columns and ten rows of reaction cavities. Each of the wells or reaction cavities will be fitted with a ball, so that when the plate will be rotated without changing its general orientation, the resulting movement for the balls within each of the wells or cavities will be circular, with constant sense of turning.

Generally speaking, the turning of each of the balls will be produced by means of a common mechanical arrangement for all of the balls, so that

there will be no need to act particularly on each of them.

Given the characteristics of the system of the invention, there will be the possibility of using discardable plates with a great quantity of reaction cavities. This will help in speeding the general process and to the reduction of the space needed.

For its better understanding, a prefered embodiment will be explained in the following with reference being made to the enclosed drawings, in which:

Figure 1 shows a block chart corresponding to the process of the present invention.

Figures 2 and 3 are a view from the top and a side view with a partial cross section of a sample carrying plate.

Figure 4 shows a pictorial view of the driving arrangement of the sample carrying plate.

Figure 5 shows a detail of the attachment of the driving motor to the sample carrying plate.

Figures 6 and 7 show examples of the arrangement of the image capturing camera.

Figure 8 is a simplified top view of the means to place the sample on the reaction cavities.

Figure 9 shows a simplified view of the means for feeding the reaction products to the wells of the cavity carrying plate according to the invention.

The process of the present invention comprises the arrangement of the elements shown in the block chart of figure 1, duly related among themselves so that a TV camera -40- may capture the images of plate -37- carrying the reaction avities in which the different samples have been fed from a sample preparation device -34-. The feeding of the reaction products will be carried out by means of a proportioner device -35-. The sample preparing device -34- will receive sample -32- and the proportioner -35- will receive separately the reaction products -33-. Temperature will be controled by a temperature controling means -31- which will act on all elements under consideration, that is, the samples and sample preparing device, reaction products and proportioner device as well as the plate carrying the reaction cavities. The informations being captured by the TV camera -40-, will pass to data preparation step -41- to be relayed to an image processor -42-. Thereafter, the computer -43- will process the data to be fed to standard computer systems -44-.

A processor -36- will carry out the control of the process on the sample preparation device -34-, proportioner -35 and the system for the automatic feeding and discarding of plate -38- as well as the driving means -39- for the rotation of the plates carrying the reaction cavities. The system for the process control with receive the feed-back from the computer -43-.

The apparatus to carry out the process will essentially comprise a plate -1- carrying a series of wells or cavities -2- for the samples distributed according to a pattern which usually will correspond to straight columns and rows as shown in the drawing or any other pattern adapted to the apparatus. Each of the cavities or wells will receive from one side a sample of the fluid to be analyzed, that is, of the blood or plasma which coagulation velocity is to be determined and from the other side it will receive the reaction products to be used to enhance coagulation.

In order that the apparatus may be suitable for carrying out the process of this invention, it will be essential that each cavity -2- has mechanical means to sense the physical variations of the fluid to be analyzed at the moment in which coagulation is initiated. In the drawings, a prefered embodiment has been shown in which each of the wells or cavities has one ball -3-.

The driving of plate -1- will be preferably carried out so that the mechanical means aimed at sensing the start of the coagulation may be subjected to a turning movement in only one direction. To this end, it is possible to have one driving motor -4- with a corresponding first pulley -5- which by means of a belt, is capable to drive a second end pulley -7- which has an excentrical shaft -8- articulated on platform -10- which supports the cavity carrying plate -1-. In this way, the plate will have a circular movement in only one sense, so that in any point on the plate, the movement will correspond to turning in only one direction, as it has been shown by arrow -9- in figure 5.

For better timing of the movement of the platform and the cavity carrying plate supported on the platform, the belt -6- will be a toothed belt, the same as pulleys -5- and -7-.

Platform -10- receives the cavity carrying plate by means of rims -11-, -12-, -13- and -14-, shown only as an example. The platform has at the same time a series of holes -15- to allow the observation of cavity -2- of plate -1-from the bottom.

According to this invention, a TV camera is provided for capturing images. The TV camera will be located under the plateform, directed towards the upper part as in the version shown in figure 6, in which the camera has the reference numeral -16-. The camera could also be laterally located with the combination of a mirror, such as in the version shown in figure 7, in which the TV camera -17- captures the images through mirrors -18-.

According to the present invention, the apparatus will be completed by means of a reactive preparation system which has been schematically shown in figures 8 and 9. The reactive preparation system is constituted by a support for a series of reactive despensing nozzles, each of which is con-

nected to a peristaltic pump for the reactives by a pipe ending in the corresponding container.

The support has been shown schematically by means of plate -19- which bears multiple holes -20- for receiving the nozzles which have received reference numeral -21- in figure 9, and which movement may be obtained by a double arm system as shown by -22- and -23-. A series of containers -24- for the reactives will supply the reactives to nozzles -21- intermediate peristaltic pumps -25-shown in figure 9.

The driving system for plate -19- will have a movement according to three coordinated axis to obtain the necessary displacements in relation with the cavities of the plate, to allow the charging of the reactives on the same.

The TV camera will be connected to an image processing system composed by a capturing and digitation means and by signal processing means. The result will be the determination of the moment in which an alteration in the movement of each ball will appear.

The memory of the system will have a representation on real time of the image corresponding to the real view or scene. This information has to be processed by means of algorithms related to specific electronic circuits.

Complementarily, the apparatus of this invention will comprise means for the illumination of the scene, as well as for the thermostatic control of the plate carrying the reactives, as well as other auxiliary conventional means.

Although the invention has been shown in relation with a prefered embodiment, it is to be understood that the technicians skilled in the matter may contrive new executions to be comprised within the broad scope of the following claims.

Claims

1. Process and apparatus for the determination of the coagulation time of blood and plasma which comprises mechanical means contacting the fluid and the corresponding reactives to be analyzed, which mechanical means are given a displacement which is capable to be altered by the initiation of the coagulation of the fluid to be analyzed, wherein the images in real time of the mechanical means under displacement within the fluid to be analyzed are obtained by means of a television camera, being transmitted to a computer which is capable to analyze the images to derive from the same the variation of one or more parameters related with the alteration of the movement of the mechanical means as a function of the initiation of the coagulation.

2. Process and apparatus for the determination of the coagulation time of blood and plasma according to claim 1, wherein the apparatus has support plates having multiple cavities for the samples and the reactives to be analyzed, the plate being transparent, to allow the optical observation by the image capturing camera, being the plate capable to be attached to a platform which has a circular movement in only one direction in all and each of its points.

3. Process and apparatus for the determination of the coagulation time of blood and plasma according to claim 2, wherein the support for the plate is effected with a turning movement by means of its attachment to an excentrical means in one point which is remote relative the articulation of the plate, allowing the same turning movement in only one sense to be obtained, in each and all points of the plate.

4. Process and apparatus for the determination of the coagulation time of blood and plasma according to claim 2, wherein the apparatus has a reactive feeding system with a number of nozzles associated a support which is driven in three dimensions to allow the charge of the various reactives in each of the sample containing wells of a plate, the reactives being channeled by means of pipes from the corresponding containers intermediate respective peristaltic pumps.

5. Process and apparatus for the determination of the coagulation time of blood and plasma according to claim 2, wherein the TV camera for capturing images in real time is attached to the apparatus in a form that its field of vision covers all of the sample cavities in the support plate from a unique point of vision, preferably from underneath of the sample carrying plate.

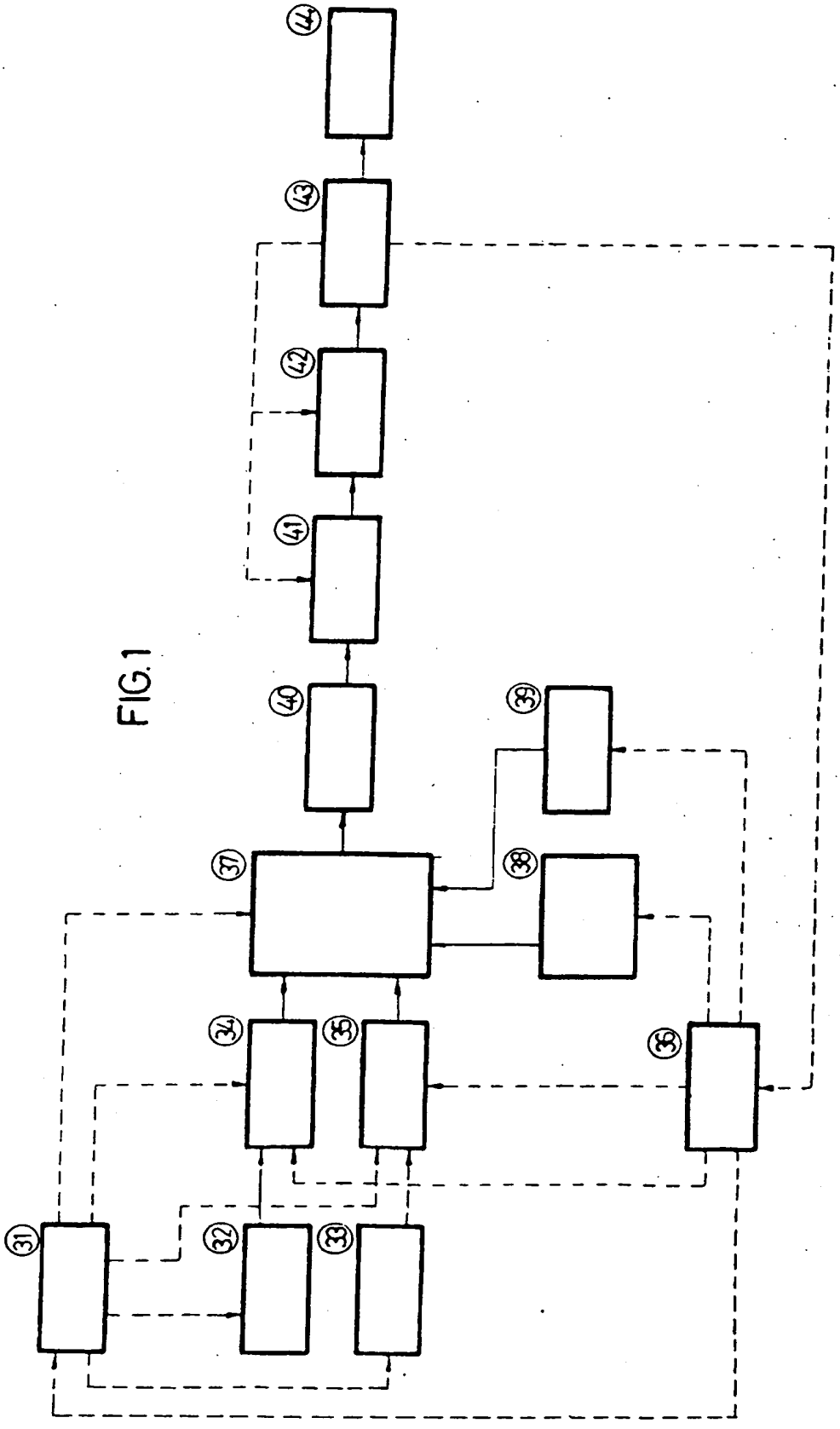


FIG.1

FIG. 2

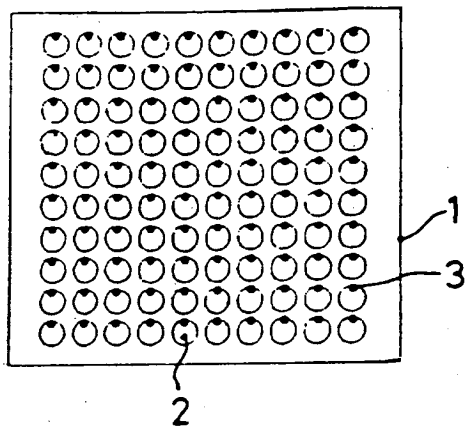


FIG. 3

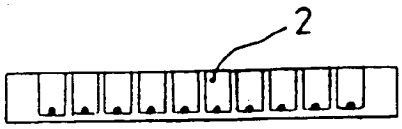


FIG. 4

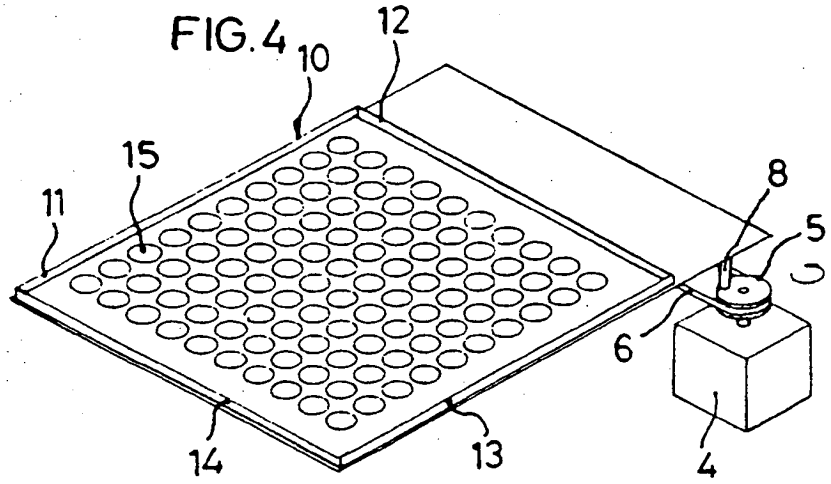


FIG. 5

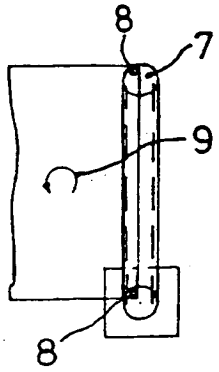


FIG. 6

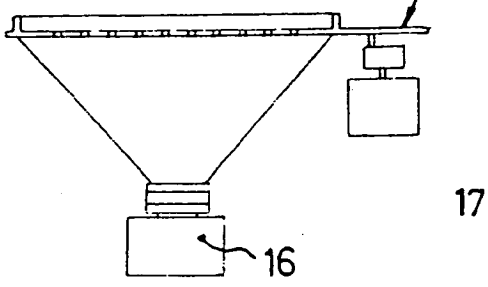


FIG. 7

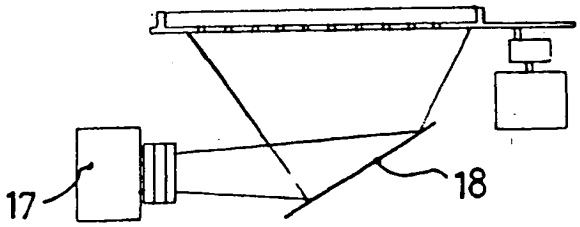


FIG. 8

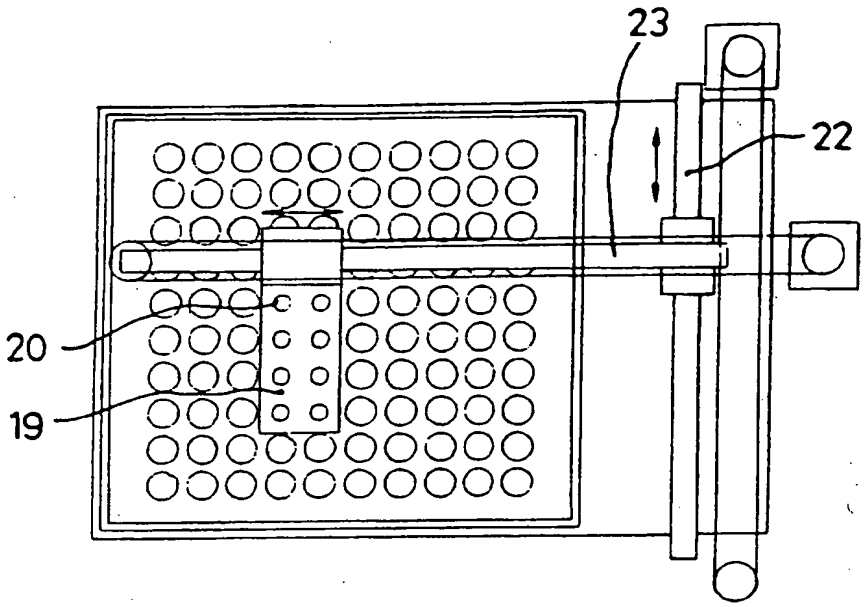
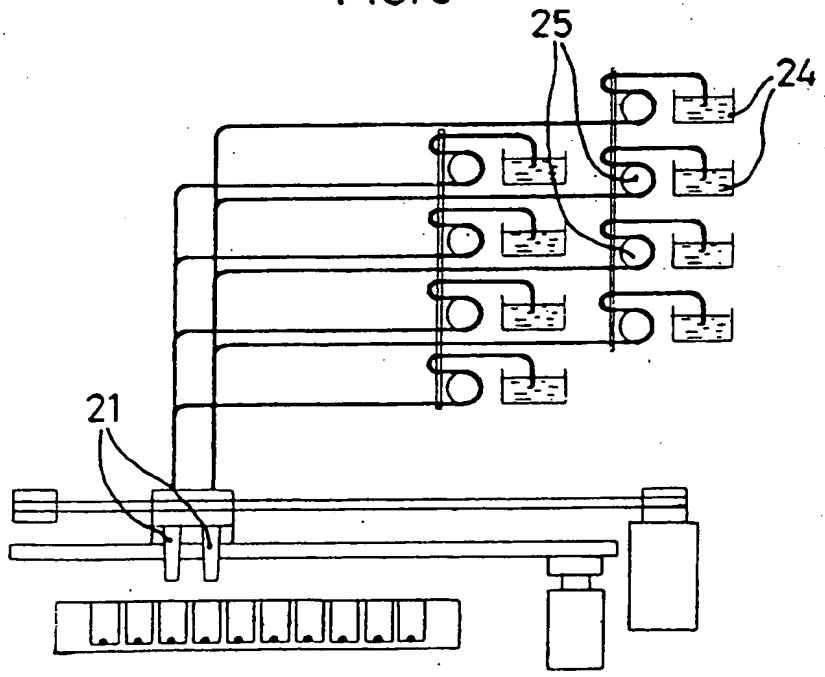


FIG. 9



European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 91 50 0089

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	DE-A-3 540 661 (HEINRICH AMELUNG GMBH) * the whole document *	1-5	G01N33/49 G01N33/86 G01N11/10
A	FR-A-2 318 421 (GIROLAMI, ANTOINE) * the whole document *	1-5	
A	PATENT ABSTRACTS OF JAPAN vol. 6, no. 59 (P-110)(937) 16 April 1982 & JP-A-57 000 552 (KOUWA K. K.) 5 January 1982 * abstract *	1-3,5	

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

G01N

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	06 APRIL 1992	DÖPFER, K.P.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P0401)